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Mechanism of Fibril Formation of Aβ_{16-22} Peptides

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Using all-atom simulations with the GROMOS96 force field 43a1 in explicit water we have studied the kinetics of fibril formation of Aβ_{16-22} peptides. These short peptides are the hydrophobic core of longer amyloid peptides which are believed to play the key role in the Alzheimer's disease. It is found that the incorporation of a newly added peptide to the preformed template obeys the two-stage dock-lock mechanism. This is in the qualitative agreement with the recent experiments.

1 Introduction

Understanding the mechanism of oligomerization of proteins and peptides remains one of the most exciting problems in structural biology because a large body of evidence suggests that amyloid fibrils and associated oligomeric intermediates are related to a number of diseases, including Alzheimer's, Parkinson's, Huntington's, and prion diseases[1]. The recent experiments of different groups (see, e.g. Ref. 2 and references therein) suggest that the addition of soluble Aβ and Sup35 amyloid monomers to preformed fibril structures is a two-stage dock-lock process. First the added peptide docks into the template and at this stage its structure gets elongated. In the slow lock phase its orientation fluctuates a lot before reaching the fibril state. Motivated by these interesting experiments we have studied the process of incorporation of a Aβ_{16-22} peptide into the preformed template using the all-atom simulations by GROMACS software[3]. Namely, we have considered[4] the reaction $(\mathrm{A}\beta_{16-22})_{n-1} + \mathrm{A}\beta_{16-22} \rightleftharpoons (\mathrm{A}\beta_{16-22})_n$, where $n = 4, 5$ and 6. In this contribution we presents the results for the $n = 5$ case (pentamer) where a monomer adds to the preformed fibril state of 4 peptides. Our results support the two-stage picture in which the lock phase is much slower than the initial dock phase.

2 Method and Results

The procedure of generating the template of 4 preformed peptides (see Fig. 1a) may be found in Ref. 4. The conformation of monomeric Aβ_{16-22} was extracted from the structure of Aβ_{10-35} peptide available in the Protein Data Bank (ID: 1hz3). Then we have added it

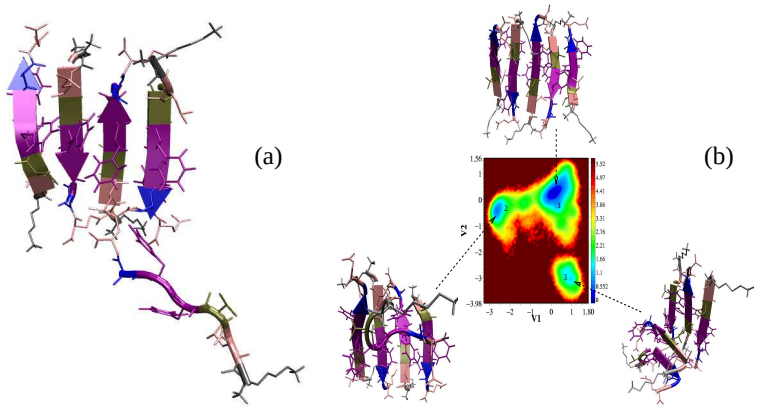

Figure 1. (a) A initial conformation of the pentamer, where one peptide is randomly added to the template of four ordered monomers. (b) The free energy landscape as a function of V_1 and V_2. The typical conformations of main local minima are shown.

randomly to the template (1a) and generated four trajectories of 329, 360, 540 and 737 ns using the GROMOS96 force field 43a1 in explicit water. A typical initial configuration is shown in Fig. 1a. The volume of the simulation box is 128 nm^3 which corresponds to the peptide concentration of 65 mM.

In order to monitor the fibril formation process we use the "liquid crystal" order parameter P_2. If $P \geq 0.9$ then the system is considered to be in the fibril-like state[4]. We used the dihedral principal component analysis[4] to compute the free energy landscapes (FEL) using the first two eigenvectors V_1 and V_2. To show that the added peptide incorporates into the preformed monomers by the dock-lock mechanism we monitor the time dependence of the β-content, $\beta(t)$, which has been computed using the definition, given in Ref. 4.

Fig. 1b shows the free energy as a function of V_1 and V_2. The fibril-like arrangement is found in the basin of the most prominent minimum 1 which has $\approx 67\%$ of population. Since three local minima are separated by low barriers of only a few k_BT the system is not stable under thermal fluctuations. The stability gets enhanced as the number of peptides increases[4].

The time dependence of the order parameter P_2 for the entire system and the preformed 4 peptides is shown in Fig. 2. Remarkably the template fluctuates a lot to accommodate the added monomer. This is probably because the number of monomers is lower than the size of the critical nucleus which remains largely unknown for the Aβ_{16-22} system but our recent analysis has shown that this size should be at least larger than six. If we define the time for adding a new monomer, t_{add} as the time needed to get $P_2 = 0.9$ for the entire system then $t_{add} \approx 110$ ns for the pentamer (the result is averaged over four trajectories).

From the time dependence of the content of the beta content, $\beta(t)$ (Fig. 3a), it follows that the nascent peptide docks into the the preformed subsystem first. Namely, initially $\beta(t)$ of the disordered monomer is lower than that of the preformed subsystem and they become compatible at the end of the dock phase. In order to get into the fibril state the added peptide spends a lot of time on its reorientation while the preformed template fluctuates to accommodate it. As evident from Fig. 3b the accumulated value $\overline{\beta}(t)$ of the nascent

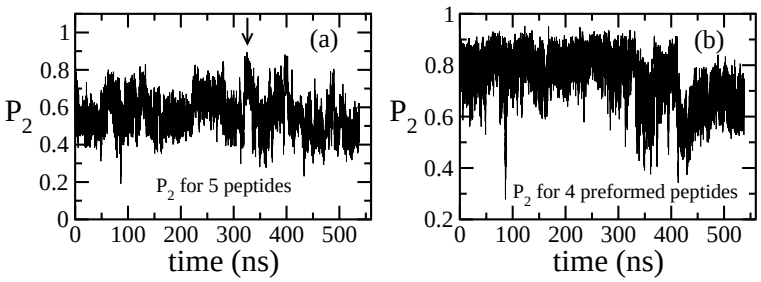

Figure 2. (a) Time dependence of P_2 for the whole system of 5 peptides. The arrow refers to $P-2 \approx 0.9$ which corresponds to the adding time. (b) The same as in (a) but for the preformed template.

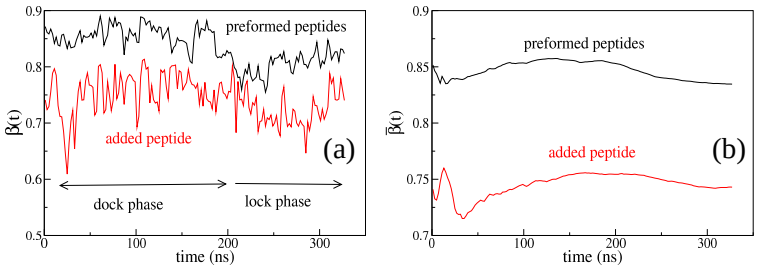

Figure 3. (a) The time dependence of the beta content of the preformed four peptides (black) and the added monomer (red). (b) The same as in (a) but for $\overline{\beta}(t) = \frac{1}{t}\int_0^t \beta(x)dx$.

monomer approaches the value of the template very slowly, the second lock phase should have much longer time scale compared to the dock stage.

In conclusion, we have shown that the fibril formation of short peptides obeys the two-stage dock-lock mechanism. This may be also valid for longer peptides and proteins.

Acknowledgments

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References

1. F. Chiti, and C. M. Dobson, *Protein misfolding, functional amyloid, and human disease*, Annual Rev. Biochemistry **75**, 333–366, 2006.
2. R. S. Collins, A. Douglass, R. D. Vale, and J. S. Weissman, *Mechanism of prion propagation: Amyloid growth occurs by monomer addition* PLOS Biol. **2**, 1582-1590, 2004.
3. H. J. C. Berendsen, D. van der Spoel and R. van Drunen, *A message-passing parallel molecular dynamics implementation*, Comp. Phys. Comm. **91**, 43–56, 1995.

4. P. H. Nguyen, M. S. Li, G. Stock, J. E. Straub, and D. Thirumalai, *Monomer adds to preformed structured oligomers of Aβ-peptides by a two-stage dock-lock mechanism*, Proc. Natl. Acad. Sci. USA **104**, 111–116, 2007.